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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/629,074	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,17-19,21-23,25-33 and 36-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10,17-19,21-23,25 and 29* is/are rejected.

7)☒ Claim(s) *4,9,11,12,26-28,30-33 and 36-43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed July 16, 2003 (Paper No. 19) has been entered. Claims 1-3, 6, 19, 21, 26, and 37-43 have been amended. Claims 20, 34, and 35 have been cancelled.

Accordingly, Claims 1-12, 17-19, 21-23, 25-33, and 36-43 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

The rejection of Claims 1-12, 17-21, 26, and 34-43 under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicants' amendment. The claims have been amended so that they are now limited to an **adenoviral vector** encoding VEGF (and at least one osteogenic protein) or a method of using an **adenoviral vector** encoding VEGF.

However, upon further consideration, a new ground(s) of rejection is made in view of WO95/24473, U.S. Patent No. 5,935,820, U.S. Patent No. 6,398,816, U.S. Patent No. 6,525,030, and U.S. Patent No. 6,475,480.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 6, 17-19, 21, 22, and 25 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over WO95/24473 (Hu et al.).

The claims are directed to a method for enhancing bone density or formation by administering to at least one first cell within a bone or within a tissue immediately surrounding a bone an adenoviral vector comprising at least one first nucleic acid encoding a vascular endothelial growth factor, such that the first nucleic acid is expressed in the cell to produce the vascular endothelial growth factor, whereby bone density or formation is enhanced within the region. Claim 18 specifically provides for the embodiment where the first nucleic acid and the second nucleic acid are the same nucleic acid. Claim 19 is directed to an adenoviral vector comprising at least one first nucleic acid encoding a vascular endothelial growth factor and at least one second nucleic acid encoding at least one osteogenic protein. However, given the language of Claim 18 the second nucleic acid referred to in Claim 19 may encode VEGF as well. Claim 22 is directed to a bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding a vascular endothelial growth factor and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein. As discussed above, the second nucleic acid referred to in Claim 22 need not encode a distinct protein, but may also encode VEGF.

Hu et al. discloses a polynucleotide encoding VEGF2. The reference further describes using the disclosed polynucleotide encoding VEGF2 "to promote growth of damaged bone and tissue" (page 4, paragraph 3). At page 17, paragraph 2, the reference discloses that VEGF2 may be used to induce the growth of damaged bone. Moreover, the reference specifically mentions using adenovirus to deliver a polynucleotide encoding VEGF2 (page 18, paragraphs 3-5). It discloses that cells may be transduced with the polynucleotide *ex vivo* (as recited in Claim 3 of the instant application) or *in vivo* (as recited in Claim 2 of the instant application). Claim 21 of Hu et al. is directed to treating a patient in need of VEGF2 by administering DNA encoding VEGF2.

Thus, the claimed invention is disclosed in the prior art.

Claims 1-3, 5, 6, 17-19, 21, 22, and 25 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,935,820 (Hu et al.).

Hu et al. discloses a polynucleotide encoding VEGF2. The reference further describes using the disclosed polynucleotide encoding VEGF2 "to promote growth of damaged bone and tissue" (Column 2, lines 38-42). At Column 9, lines 57-58, the reference discloses that VEGF2 may be used to induce the growth of damaged bone. Moreover, the reference specifically mentions using adenovirus to deliver a polynucleotide encoding VEGF2 (Column 10, lines 34-55). It discloses that cells may be transduced with the polynucleotide *ex vivo* (as recited in Claim 3 of the instant application) or *in vivo* (as recited in Claim 2 of the instant application).

Thus, the claimed invention is disclosed in the prior art.

Claims 1, 3, 6-8, 17, 18, 22, 23, 25, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,398,816 (Breitbart et al., filed September 4, 1997).

Breitbart et al. disclose the use of genetically engineered cells expressing a number of specific bioactive molecules for bone repair. The claims specifically recite that "the cells are applied to or incorporated into a prosthesis for repair or replacement of bone, cartilage, or connective tissue" (see Claim 1). The claims further recite that the cells are genetically engineered to express an effective amount of growth factors "selected from the group consisting of platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (FGF), insulin-like growth factor (IGF), endothelial derived growth supplement (EDGS), keratinocyte growth factor (KCF), osteogenin, skeletal growth factor (SGF), osteoblast-derived (BDGFs), retinoids, growth hormone (GH), bone morphogenic proteins (BMPs), and transferrin" (see Claim 5). Claim 9 is specifically directed to periosteal cells genetically engineered to express BMP-7. The specification discloses that genetically engineered periosteal cells are to be used for repair of bone (see abstract at lines 6-8). The specification further discloses that cells can be implanted directly into a defect in an amount effective to promote repair (Column 8, lines 38-39). The specification makes it clear that the invention covers cells transfected with more than one of the genes mentioned in the claims. For example, at Column 3, lines 41-43, the specification states that "for repair of bone, a gene **(or genes)** encoding bone morphogenic protein is transfected into periosteal cells." Furthermore, the claims recite "bioactive molecules" in the plural form. The specification discloses using adenoviral vectors to transduce the cells (Column 8, lines 8-10).

Thus, the claimed invention is disclosed in the prior art.

Claims 1, 2, 6-8, 10, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,525,030 (Eriksson, filed December 15, 1997) and U.S. Patent No. 6,475,480 (Mehtali et al., filed July 6, 1999).

Eriksson discloses a method for stimulating bone growth by repeatedly injecting expressible genetic material encoding a product that modulates bone growth into periosteal cells (see especially Claim 3). The specification discloses that a preferred gene for delivery can include a gene that encodes a product that can modulate bone growth, which products can include cytokines and those listed in Table 3 (Column 16, line 66 to Column 18). Many of the genes listed in Table 3 are also recited in Claim 2. Furthermore, it is noted that Claim 2 recites "and a combination of any of the foregoing." Such combinations would meet the limitations of the instant claims when VEGF is included. The specification specifically states that a plurality of genes may be delivered in combination (Column 18, lines 4-5).

Mehtali et al. disclose an adenoviral vector which provides for improved expression of its cargo gene. The reference discloses a method for improving the expression and/or persistence of expression of a gene of interest in a mammal (see especially Claim 18).

Given that Eriksson discloses a method for stimulating bone growth by administering a gene to a periosteal cell and further given that Mehtali et al. discloses a method for improving the expression of a gene of interest in a mammal by using a specific type of adenoviral vector, one of skill in the art would have been motivated to employ the use of the adenoviral vector of Mehtali et al. in the method of Eriksson to boost the expression of the gene that will stimulate bone growth. Given that only standard molecular biology techniques are required to prepare an adenoviral vector as taught by Mehtali et al. carrying any gene of interest, one of skill in the art would have anticipated a reasonable expectation of success for making the necessary adenoviral vectors and using them in the method disclosed by Eriksson.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Allowable Subject Matter

Claims 4, 9, 11, 12, 26-28, 30-33, and 36-43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER